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Docket No. 10806-151

PATENT

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Lauren E Mauz

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Andreas CASTAN	:	Paper No.:
Serial No.:	09/732,638	:	Group Art Unit: 1655
Filed:	December 8, 2000	:	Examiner: B. Sisson
For:	**Production of Peptides**		

AMENDMENT

Box RCE
Commissioner for Patents
Washington, D. C. 20231

Dear Sir:

In response to the Official Action dated December 18, 2001, please amend the present application as follows:

In the Claims:

Please cancel claim 21.

Please amend claims 1 and 23 to read as follows:

C1

1. (Third Amendment) Method for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts, wherein the cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period, wherein the oscillation amplitude has a wave period of from about 1 to about 30 minutes, wherein the microorganism is a biological host selected from the group

consisting of bacteria, yeast and animal cell, and wherein the cultivation conditions remain aerobic.

C2 23. (Amended) Method according to claim 1, wherein the oscillation feed has a wave amplitude of from about +/- 5% to +/- 60% of standard.

Please add claim 28 to read as follows:

C3 28. (New) Method according to claim 1, wherein the oscillation feed and/or oscillation variation in stirring speed is from about +/- 5% to +/- 60% of standard.

REMARKS

The Official Action dated December 18, 2001 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claim 21 is canceled. Claim 1 is amended to clarify the method for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts, in accordance with the teachings as set forth in the specification at page 5, lines 1-2, 12 and 17-21. Claim 23 is amended as to a matter of form, and claim 28 is added, support for which may be found at page 5, lines 20-21 of the specification. A Version With Markings Showing Changes Made is attached. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

Claims 1-27 were rejected under 35 U.S.C. §112, first paragraph, as not being enabled by the specification. The Examiner asserted that the specification does not provide enablement for achieving the unexpected physiological result when culturing is conducted under different parameters; e.g., different carbon sources, oscillation agitation speed, or oscillation means. In addition, the Examiner asserted that the method of claim 1 has been characterized by an oscillation variation of stirring speed where the components of the culture media are allowed to go to exhaustion.

However, as will be set forth in detail below, Applicant submits that the methods defined by claims 1-27 are fully enabled to one of ordinary skill in the art, in accordance with the requirements of 35 U.S.C. §112, first paragraph. Accordingly this rejection is traversed and reconsideration is respectfully requested.

More particularly, claim 1 recites a method for the production of recombinant peptide by fed-batch cultivation of a microorganism in a bioreactor containing a medium comprising organic carbon source, nitrogen source and mineral salts. The cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed, without exhaustion of the organic carbon source during the oscillation period. The oscillation amplitude has a wave period of from about 1 to about 30 minutes. The microorganism is a biological host selected from the group consisting of bacteria, yeast and animal cell. The cultivation conditions remain aerobic.

Thus, the methods of claim 1 are directed towards the production of recombinant peptide by fed-batch cultivation wherein the oscillation amplitude wave period, microorganism and cultivation conditions are specifically defined in accordance with the teachings at page 5 of the specification. Further, Applicants note that the cultivation defined by claim 1 is carried out without exhaustion of the organic carbon source during the oscillation period.

As recombinant human proteins are important pharmaceuticals, methods for the production of recombinant peptides by fed-batch cultivation of a microorganism in a bioreactor are well known in the art. The inventor has determined a novel method for improved peptide production when the carbon source is varied in oscillation feed and/or stirring speed is performed in oscillation variation in a fed-batch cultivation. Specific and enabling details of the method for the production of recombinant peptide as claimed are set forth in the specification at page 1, lines 6-10 and pages 5-7. Further, the specification discloses specific embodiments of the claimed method as set forth on pages 6-7. As the oscillation amplitude wave period, microorganism and culture conditions are specifically defined in the claims and disclosed in the specification, one of ordinary skill in the art will easily appreciate that the method for the production of recombinant peptide as disclosed and claimed may be employed without undue experimentation.

As a matter of Patent Office practice, a specification disclosure which contains a teaching of a manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of section 12 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on enabling support, *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (CCPA 1971) (emphasis by Court). A disclosure is enabling if, from the information set forth in the specification, coupled with information known in the art, one of ordinary skill in the art could make and use the invention without undue experimentation, *United States v. Teletronics, Inc.*, 8 U.S.P.Q.2d 1217, 1224 (Fed. Cir. 1988). Moreover, every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification; rather, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention, *Genetech v. Novo Nordisk, A/S,* 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). Furthermore, Applicants are not required to disclose every embodiment encompassed by their claims, even in an unpredictable art. *In re Angstadt,* 190 U.S.P.Q. 214 (CCPA 1976).

One of ordinary skill in the art will appreciate fed-batch cultivation methods are known in the art to produce recombinant peptides. The present specification provides the teaching of the manner and process of making and using the inventive production method in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented. Moreover, the Examiner has not provided any objective evidence of record which is inconsistent with the teachings of the specification relied upon for enabling support. Accordingly, the present specification must be taken as enabling for the methods for the production of recombinant peptides as defined by claims 1-27, *In re Marzocchi*, supra. It is therefore submitted that the rejection under 35 U.S.C. §112, first paragraph, has been overcome. Reconsideration is respectfully requested.

Claims 1-27 were rejected under 35 U.S.C. §102(f) on the basis that the Applicant did not invent the claimed subject matter. The Examiner asserted that Bylund et al, "Influence of Scale-Up on the Quality of Recombinant Human Growth Hormone", *Biotechnology and Bioengineering*, Vol. 69, No. 2, July 20, 2000 (Bylund et al) disclose a method for the recombinant production of peptides by fed-batch cultivation of a microorganism in a bioreactor. Specifically, the Examiner asserted that Figure 2 of Bylund et al clearly depicts the different oscillations of organic carbon source concentrations. Finally, the Examiner asserted that since Applicant was co-author of Bylund et al, a reasonable question exists as to what inventive contribution the other individuals, G. Larsson and F. Bylund, had toward the claimed invention.

However, as will be set forth in detail below, Applicant submits that the methods defined by claims 1-27 were invented solely by the Applicant, and that the claimed methods were not invented by and are not taught by Bylund et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

A noted above, claims 1-27 are directed to methods for the production of recombinant peptide by fed-batch cultivation of a microorganism. The cultivation is carried out by the addition of the organic carbon source in oscillation feed and/or by oscillation variation of stirring speed.

In contrast, Applicant finds no disclosure in Bylund et al of the presently claimed methods. Specifically, Bylund et al disclose aerobic fed-batch production of recombinant peptides where the feed profile of the carbon source consisted of three different phases: an exponential feed, a constant feed and a decrease of feed, as disclosed on page 121, left column. The variation of the feed profile is for determining the accuracy of the glucose feed and is not related to a variation in the feed. Further, Figure 2 of Bylund et al depicts a variation of the glucose concentration which is due to insufficient mixing and the scale-up

situation, *not* to oscillations of organic carbon source feed. Specifically, the close position of sampling relative to feed point is due to the fluctuation between samples and occasionally higher concentrations measured and not oscillations of organic carbon source.

Since Bylund et al do not disclose oscillation feed or oscillation variation in stirring speed in a cultivation procedure as presently claimed, there is no basis to assert that G. Larsson and F. Bylund provided inventive contribution toward the claimed invention, or, conversely, to assert that the present Applicant did not invent the claimed invention. It is therefore submitted that the rejection under 35 U.S.C. §102(f) has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Examiner's rejections under 35 U.S.C. §§102 and 112, first paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are respectfully requested.

Respectfully submitted,

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